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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/077,065	02/15/2002	Venita I. DeAlmeida	P1872R1	3480

7590 09/26/2005

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EXAMINER	
EWOLDT, GERALD R	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 09/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/077,065	DEALMEIDA ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 July 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) *10-41 and 46-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 42-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's remarks filed 7/07/05, are acknowledged.

2. Claims 10-41 and 46-52 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b).

Claims 1-9 and 42-45 are pending and under examination.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-9 and 42-45 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the specification provides insufficient evidence that the claimed method could be used to effectively treat insulin resistance or hypoinsulinemia, or be used to repair or regenerate muscle in a mammal.

As set forth previously,

The method of the instant claims presumably functions by employing an antagonist of Dkk-1, such as an antibody, such that Dkk-1 is unavailable for the downregulation of Wnt family proteins. Thus, it is actually the upregulation (or lack of downregulation) of Wnt proteins that would provide the treatment of insulin resistance or hypoinsulinemia, or the repair or regeneration of muscle. The specification implies that Wnt proteins activate numerous other proteins involved in the insulin-signaling cascade or the differentiation of myocytes into adipocytes. Presumably, upregulating Wnt proteins would upregulate downstream effectors leading to increased insulin metabolism and decreased differentiation of myocytes into adipocytes (which would presumably result in the repair or regeneration of muscle).

A review of the specification discloses just a single relevant example (Example 1) supporting the method of the instant claims. The example discloses that the culture of L6 myoblasts in a medium including Dkk-1 causes reduced insulin-stimulated glucose uptake, while the culture of 3T3/L1 fibroblasts in a medium including Dkk-1 causes increased insulin-stimulated glucose uptake and the decrease in the expression of some markers that would indicate adipocyte differentiation in said cells. The disclosure also teaches that the injection of Dkk-1 into mice causes altered expression of muscle specific genes and reduces insulin secretion, and that overexpression of *dkk-1* in transgenic mice causes reduced size and bodyweight in the animals. It is unclear how this disclosure is intended to enable the method of the instant claims.

The specification fails to disclose that, like many developmental genes, Wnt family genes are both developmental genes and proto-oncogenes (see for example, Behrens et al. 2004). As taught by LeFloch et al. (2005), "Inappropriate expression of Wnt/APC/β-catenin signaling pathways plays a critical role at the early stages in a variety of human cancers". Uematsu et al. (2003) "identified Wnt signaling in thoracic malignancies", including mesothelioma and non small cell lung cancer. Chen et al. (2003) links Wnt signaling to melanoma progression. Miyoshi et al. (2002) teaches that Wnt expression induces mammary tumors.

Regarding Dkk-1 in particular, Wang et al. (2000) show that p53 exhibits its tumor suppressor activity through Dkk-1-mediated downregulation of the Wnt signaling pathway. In a mesothelioma model, Lee et al. (2004) show that Dkk-1 exerts a tumor suppressive effect by antagonizing Wnt signaling. Finally, Gonzalez-Sancho et al. (2005) teach, "Our data indicate that the Wnt/β-catenin pathway is regulated by the induction of DKK-1 expression, a mechanism that is lost in colon cancer".

Clearly then, these combined teachings would not lead one of skill in the art to conclude that the downregulation of Dkk-1, causing the upregulation of Wnt, would be a good idea. While the specification provides some inconclusive teachings regarding the efficacy of a Dkk-1 antagonist for the treatment of insulin resistance or hypoinsulinemia, or the repair or regeneration of muscle, the prior art clearly teaches that the downregulation of Dkk-1, causing the upregulation of Wnt, would exacerbate, if not actually induce, any number of cancers - conditions far worse than the conditions the claimed method is intended to treat. Accordingly, it is the Examiner's position that the invention of the instant claims would require undue experimentation to practice as claimed.

Applicant's arguments, filed 7/07/05, have been fully considered but they are not persuasive. Applicant reviews the teachings of the disclosure and argues that said disclosure enables the claimed method. Applicant submits Tian et al. (2003) and an additional article from *Reuters Health* in support of the claimed invention.

As set forth above, the enablement of the disclosure is not commensurate with the scope of the claimed invention. The limited teachings of the disclosure include *no* data involving the use of Dkk-1 antagonists either *in vivo* nor even *in vitro*. The limited teachings disclose that when two cell types were incubated with excess Dkk-1 they acted in opposite manners, i.e., the culture of L6 myoblasts in a medium including Dkk-1 caused reduced insulin-stimulated glucose uptake, while the culture of 3T3/L1 fibroblasts in a medium including Dkk-1 caused increased insulin-stimulated glucose uptake. Clearly then, even in the simplest of model systems, the specification itself establishes that Dkk-1 has an unpredictable effect on insulin-stimulated glucose uptake.

It was also established in the previous Office action that the *in vivo* processes involving Dkk-1 and Wnt expression are likely considerably more complex than might be assumed from a

reading of the instant specification. No less than eight references were cited in support of this position. Applicant has countered with a reference wherein it is taught that Dkk-1 is an inhibitor of osteoblast differentiation and is associated with bone lesions in multiple myeloma patients. It is unclear how this teaching supports a method of treating insulin resistance or repairing muscle comprising administering a Dkk-1 antagonist. If anything, the reference further demonstrates what was previously established, i.e., that Dkk-1 is involved in multiple physiological processes.

Applicant argues that "undesirable side effects" do not comprise a basis for questioning the enablement of a method of treating a medical disorder.

It is the Examiner's position that the induction or exacerbation of cancer comprises more that a mere "undesirable side effect" in a method of treating insulin resistance or repairing muscle.

Finally regarding the citing of an article in *Reuters Health* which, "quotes a physician from the University of Arkansas", Applicant's argument is both factually incorrect as well as misleading. First, Dr. John D. Shaughnessy Jr. is not a physician, and second, he is also the senior author of the Tian et al. reference and he is discussing his own work. It is clear that the research does not involve treating insulin resistance nor repairing muscle, and it is also clear that the inhibition of Dkk-1 has not risen to the level of invention but is merely still an idea, "The researchers are currently [2003] in the early phases of developing and testing several compounds aimed at disabling Dkk-1".

Accordingly, it remains the Examiner's position that the method of the instant claims would require undue experimentation to practice as claimed.

5. No claim is allowed.

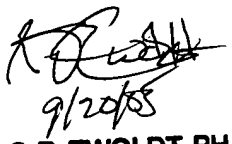
6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action

is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

8. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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